CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019651/S005

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

EXCLUSIVITY SUMMARY for NDA # 19-651 SUPPL # 005

Trade Name Asacol **Generic Name** mesalamine
Applicant Name Procter & Gamble **HFD-** 180

Approval Date 8/18/97

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?
   YES / / NO /X/

   b) Is it an effectiveness supplement?
   YES /X/ NO / /

   If yes, what type? (SE1, SE2, etc.) SE1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")
   YES /X/ NO / /

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   n/a

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   n/a

d) Did the applicant request exclusivity?

YES / X / NO / ___ /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES / ___ / NO / X /

If yes, NDA # _____ Drug Name_____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES / ___ / NO / X /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

APPEARS THIS WAY
ON ORIGINAL

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X/ NO /__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 19-919 Rowasa (mesalamine) Supp

NDA # 19-618 Rowasa enema (Rectal Susp)

NDA # 20-049 Pentasa (mesalamine) Capsules

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /__/ NO /__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # n/a _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO /___/

APPEARS THIS WAY
ON ORIGINAL

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /X/ NO /__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /__/ NO /X/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /__/ NO /__/ n/a

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 870860-862. 18. 01.

Investigation #2, Study # _____

Investigation #3, Study # _____

APPEARS THIS WAY
ON ORIGINAL

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /X/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /X/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

APPEARS THIS WAY
ON ORIGINAL

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # 870886-842.18.01

Investigation #_, Study # _____

Investigation #_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /X/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /X/

If yes, explain: _____

_____

_____

_____

_____ 8/18/97
Signature Date
Title: Reg. Health Proj. Manager

/S/ 8-18-97
Signature of Division Director Date
Acting

cc: Original NDA Division File HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 19-651 Supplement # 005 Circle one: (SE1) SE2 SE3 SE4 SE5 SE6

HFD-180 Trade and generic names/dosage form: Asacol (mesalamine) Tablets Action: (AP) AE NA

Applicant Procter & Gamble Therapeutic Class IBD

Indication(s) previously approved active treatment - ulcerative colitis (UC)
Pediatric information in labeling of approved indication(s) is adequate ___ inadequate X

Indication in this application maintenance of remission - UC (For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

X 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use. (See attached)

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. If none of the above apply, attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

/S/ , Project Manager 8/18/97
Signature of Preparer and Title Date

cc: Orig (NDA)/PLA/PMA # 19-651/S-005
HFD-180 /Div File
NDA/PLA Action Package
HFD-006/ SOImstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised 3/12/97)

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 18, 1997

FROM: Melodi McNeil, Regulatory Health Project Manager, Division of Gastrointestinal and Coagulation Drug Products (HFD-180) /S/

TO: 19-651/S-005

NDA 19-651, sponsored by Procter & Gamble Pharmaceuticals, Inc. provides for Asacol (mesalamine) Tablets for the treatment of mildly to moderately active ulcerative colitis. Supplement -005 was submitted June 4, 1996 and provides for a new indication: the maintenance of remission of ulcerative colitis.

cc:

NDA 19-651/S-005
HFD-180/Division Files
HFD-180/McNeil

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

PATENT INFORMATION PROVIDED PURSUANT TO 21 U.S.C. 355(B)

RE: NDA #19-651 ASACOL

SUPPLEMENT FILED June 4, 1996

To the best of Applicant's knowledge, there is no issued U.S. Patent claiming the drug or a relevant method of use. However, two patent applications claiming the drug are pending in the U.S. Patent & Trademark Office. These applications are assigned to Tillotts Laboratories and licensed to the Applicant. In the event a patent issues before approval of this New Drug Application, Applicant shall amend this Application pursuant to 21 U.S.C. 355(b), to include the pertinent patent information.

Should the patent issue after this Application is approved, the Applicant will promptly notify the Agency.

EXCLUSIVITY STATEMENT

REQUESTING THREE YEARS OF EXCLUSIVITY

A. LIST OF PUBLISHED STUDIES FOR APPLYING FOR 3-YEAR EXCLUSIVITY

NEW INFORMATION-ESSENTIAL TO APPROVAL OF A MAINTENANCE OF REMISSION INDICATION FOR ULCERATIVE COLITIS

New Clinical Investigation Information

This information results from the pivotal study of this application (Study #87086-862.18.01.). This study was sponsored by Procter & Gamble Pharmaceuticals under and was recently summarized in the publication listed below.

The Mesalamine Study Group. An oral preparation of mesalamine as long-term maintenance therapy for ulcerative colitis: A randomized, placebo-controlled trial. Ann Intern Med 1996;124:204-211.

New Pooled Analysis of Previously Submitted Clinical Studies

These studies were sponsored by The individual studies were submitted previously

Dew MJ, Hughes P, Harries AD, Williams G, Evans BK, Rhodes J. Maintenance of remission in ulcerative colitis with oral preparation of 5-aminosalicylic acid. Br Med J 1982;285:1012.

Dew MJ, Harries AD, Evans N, Evans BK, Rhodes J. Maintenance of remission in ulcerative colitis with 5-amino salicylic acid in high doses by mouth. Br Med J 1983;287:23-24.

Riley SA et al. Comparison of delayed-release 5-aminosalicylic acid (mesalazine) and sulfasalazine as maintenance treatment for patients with ulcerative colitis. Gastroenterology 1988;94-1383-9.

PREVIOUSLY AVAILABLE INFORMATION

Previously available, positive-controlled (sulfasalazine) study; abstract only

Dew MJ. Maintenance of remission in ulcerative colitis with mesalazine (Asacol). Presented at Symposium, "Clinical Controversies in Inflammatory Bowel Diseases"; September 9-11, 1987; Bologna, Italy.

Previously available, published uncontrolled studies

Donald IP, Wilkinson SP. Open study of Asacol for maintenance of remission in patients intolerant of sulphasalazine. Postgrad Med J 1985;61:1047-1048.

Habal FM, Greenberg GR. Open study of Asacol for maintenance of remission in patients intolerant of sulphasalazine. Gastroenterology 1985;88:1409.

Dew MJ et al. Open study of Asacol for maintenance of remission in patients intolerant of sulphasalazine. Lancet 1983;2(8353):801

Schroeder KW et al. Oral 5-aminosalicylic acid (5-ASA) induces and maintains remission in ulcerative colitis. Gastroenterology 1987;92:A1626.

Habal FM, Greenberg GR. Treatment of ulcerative colitis with oral 5-aminosalicylic acid including patients with adverse reactions to sulfasalazine. Am J Gastroenterol 1988;83:15-19.

Pallone F et al. Safety experience with Asacol tablets in Italy: a post-marketing study. Ital J Gastroenterol 1989;21(suppl 1):13-4.

Gionchetti P, Campieri M, Belluzzi A, Grunetti G, Tampieri M et al. Maintenance treatment of Ulcerative Colitis with Oral 5-aminosalicylic acid (5-ASA) in patients unable to take sulfasalazine. Abstracts, Proc Athens Internat Meet on Inflammatory Bowel Diseases, Athens, Greece, April 19-23, 1989, Scan J Gastroenterol 24(Suppl 158):135 (# 88), 1989.

B. CERTIFICATION: SCIENTIFIC LITERATURE SEARCH

The Sponsor certifies that a through scientific literature search was performed on currently available literature pertinent to clinical study experience using Asacol.

C. CERTIFICATION: PREVIOUSLY AVAILABLE INFORMATION, NOT SUFFICIENT FOR APPROVAL FOR THE MAINTENANCE OF REMISSION INDICATION FOR ULCERATIVE COLITIS FOR ASACOL.

The Sponsor Certifies that in Sponsor's opinion, there are not sufficient published studies or publicly available reports of clinical investigation (other than the new one sponsored by the applicant) to support the approval of a maintenance of remission indication for ulcerative colitis for Asacol.

CERTIFICATION PURSUANT TO THE GENERIC DRUG ENFORCEMENT ACT OF 1992

Pursuant to 21 USC Section 355a(k)1 Applicant hereby certifies that to the best of its knowledge and belief it has not used in any capacity the services of any person debarred under subsections 21 USC Section 355a(a or b), in connection with this Application and that it will not use in any capacity the services of any person debarred under 21 USC Section 355a(a or b), in connection with this Application.

Respectfully submitted,

L. R. Versteegh, Ph.D.
Vice President
Regulatory Affairs Worldwide
Procter & Gamble Pharmaceuticals

NDA 19-651/SE1-005

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 19-651/SE1-005

JUN - 5 1997

Name of Drug: Asacol (mesalamine) Tablets

Sponsor: Procter & Gamble Pharmaceuticals

Material Reviewed

Submission Date(s): June 4, 1996, draft labeling
April 4, 1997, revised draft labeling

Receipt Date(s): June 5, 1996, draft labeling
April 7, 1997, revised draft labeling

Background and Summary Description: This application was submitted June 4, 1996 and provides for a new indication: the maintenance of remission in ulcerative colitis (UC). As pivotal efficacy support, the firm submitted a double-blind, randomized withdrawal study (study # **87076**) which compared two doses of Asacol (0.8 and 1.6 gm) with placebo (PBO). In addition, the firm submitted pooled results of four small positive control studies comparing Asacol to sulfasalazine. According to the clinical and statistical reviews, dated June 4, 1997 and April 15, 1997, respectively, neither the pooled results nor the efficacy results from the 0.8 gm dose in the PBO trial supported approval. It was decided, however, that the efficacy results for the 1.6 gm dose from Study# **87076** provided sufficient evidence to support approval of that dose.

The proposed revisions which are the subject of this review were discussed with Dr. Lilia Talarico (Acting Division Director), Dr. Robert Prizont (Reviewing Medical Officer), and Ms. Kati Johnson (Supervisor, Project Management Staff) on June 2, 1997.

Review

The submitted package insert (**draft: 4/2/97**) was compared to the currently approved insert (**coded 75200-P7, Revised April 1996**, approved August 30, 1996 with S-006). The following changes have been made:

1. CLINICAL PHARMACOLOGY section, Clinical Studies subsection:

a. This section has been further subdivided into the following sections: "Mildly to moderately active ulcerative colitis," "Maintenance of remission of ulcerative colitis," and "Study to assess the effect on male fertility."

This is an acceptable editorial revision.

b. The following paragraph has been added,

Maintenance of remission of ulcerative colitis:

"In a 6 month, randomized, double-blind, placebo-controlled, multi-centered study involving 264 patients (189 eligible for analysis), Asacol, at doses of 0.8 g/day and 1.6 g/day maintained endoscopic remission of ulcerative colitis in 40/68 (58.8%) and 38/58 (65.5%) of patients, respectively, compared to 25/63 (39.7%) of placebo recipients (p = 0.036 and p = 0.006, respectively)."

Reference to the 0.8 gm/day dose should be deleted, as discussed above. Based on the June 2, 1997 discussion referenced above, the firm should be requested to revise the preceding paragraph to state,

Maintenance of remission of ulcerative colitis:
A 6 month, randomized, double-blind, placebo-controlled, multi-center study involved 264 patients treated with Asacol 0.8 gm/day (n=90), 1.6 gm/day (n=87), or placebo (n=87). The proportion of patients treated with 0.8 gm/day who maintained endoscopic remission was not statistically significant compared to placebo. In the intention to treat (ITT) analysis of all 174 patients treated with Asacol 1.6 gm/day or PBO, Asacol maintained endoscopic remission of ulcerative colitis in 61/87 (70.1%) of patients, compared to 42/87 (48.3%) of placebo recipients (p=0.005).

The efficacy results of 4 maintenance trials that compared Asacol, at doses of 0.8 gm/day to 2.8 gm/day, with sulfasalazine, at doses of 2 gm/day to 2.4 gm/day were pooled (n=200). Treatment success, i.e. efficacy, was 59/68 (59%) for Asacol and 70/102 (69%) for sulfasalazine. Using a 90% confidence interval, ±20%, the difference in maintenance of remission between Asacol and sulfasalazine was 21% favorable to sulfasalazine.

2. INDICATIONS AND USAGE section: This section has been revised to add the maintenance of remission indication.

This is an acceptable revision.

3. PRECAUTIONS section:

a. General subsection: The first sentence of the second paragraph has been changed from,

> "Exacerbation of the symptoms of colitis thought to have been caused by mesalamine or sulfasalazine has been reported in 3% of patients in controlled clinical trials."

to

> "Exacerbation of the symptoms of colitis has been reported in 3% of Asacol-treated patients in controlled clinical trials."

Based on the June 2, 1997 discussion described above, this is an acceptable revision.

b. Renal subsection:

1). The first sentence has been revised from,

> "Renal impairment...has been reported in patients taking Asacol tablets as well as in patients taking other mesalamine products,"

to

> "Renal impairment...has been reported in patients taking Asacol tablets as well as other compounds which contain or are converted to mesalamine."

This is an acceptable editorial revision.

2). The section which reads,

> "In animal studies...renal papillary necrosis. Therefore,"

has been deleted and replaced by

> "In animal studies (rats, dogs, and monkeys), the kidney was the principal target organ for toxicity. Uncoated mesalamine administered to rats at doses of 170 mg/kg/day for 6 months caused mild histologic renal damage, and at higher doses (320-360 mg/kg/day) caused renal papillary necrosis. In dogs, renal damage and/or papillary necrosis occurred following dosing with uncoated mesalamine at 60 mg/kg/day for 1 year, and in monkeys

following a single oral dose of 500 mg/kg. There was no renal toxicity when delayed-release **Asacol** tablets were given to dogs at doses of 2 g/day for one year. This was approximately 4.5 times the recommended human dose (based on a dose of 2.4 g/day in a 50 kg person).

According to Dr. Jasti Choudary, Pharmacology Team Leader, the firm should be requested to retain the currently approved wording and submit a separate labeling supplement to provide for this change, since this revision is not necessitated by the addition of the maintenance of remission indication.

3). The sentence,

"Therefore, caution should be exercised when using Asacol (mesalamine) or other compounds converted to mesalamine or its metabolites in patients with known renal dysfunction or history of renal disease,"

has been revised to,

"While the Asacol formulation limits systemic absorption, caution should be exercised when using Asacol (or other compounds which contain or are converted to mesalamine) in patients with known renal dysfunction or history of renal disease."

Based on the June 2, 1997 discussion referenced above,

1. **The phrase, "While the Asacol formulation limits systemic absorption," should be deleted, because no documentation was provided to support it.**

2. **Reference to Asacol metabolites should not be deleted because justification for the deletion was not provided.**

The sentence should be revised to state, "Caution should be exercised when using Asacol (or other compounds which contain or are converted to mesalamine or its metabolites) in patients with known renal dysfunction or history of renal disease."

4. INFORMATION FOR PATIENTS section: The following paragraph has been added,

> "Patients should also be aware that ulcerative colitis is a chronic disease generally characterized by periods of active disease alternating with periods of remission. It is often necessary to continue medication even when the symptoms of ulcerative colitis have been controlled. Continuous therapy with **Asacol** is recommended in order to maintain remission and decrease the risk of relapse to active disease."

Based on the June 2, 1997 discussion referenced above, this paragraph should be deleted.

5. CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY section:

a. The first two sentences have been deleted and replaced with

> "Dietary mesalamine was not carcinogenic in rats at doses as high as 480 mg/kg/day, or in mice at 2000 mg/kg/day. When compared on a mg/M^2 basis, these doses are 9.3 and 12.3 times the recommended human maintenance dose of **Asacol** of 473 mg/M^2 (0.8 g/day), respectively. Mesalamine was negative in the Ames assay for mutagenesis, negative for induction of sister chromatid exchanges (SCE) and chromosomal aberrations in Chinese hamster ovary cells in vitro, and negative for induction of micronuclei (MN) in mouse bone marrow polychromatic erythrocytes. Mesalamine was also negative for SCE and MN in human lymphocytes."

According to page 40 of the pharmacology review, the firm should be asked to revise this section to state,

> **"Dietary mesalamine was not carcinogenic in rats at doses as high as 480 mg/kg/day, or in mice at 2000 mg/kg/day. These doses are 2.4 and 5.1 times the maximum recommended human maintenance dose of Asacol of 1.6 g/day (32 mg/kg/day if 50 kg body weight assumed or 1184 mg/m^2), respectively, based on body surface area. Mesalamine was negative in the Ames assay for mutagenesis, negative for induction of sister chromatid exchanges (SCE) and chromosomal aberrations in Chinese hamster ovary cells in vitro, and negative for induction of micronuclei (MN) in mouse bone marrow polychromatic erythrocytes. Mesalamine, at oral doses up to 480 mg/kg/day, had no**

adverse effect on fertility or reproductive performance of male and female rats."

b. The last sentence which reads, "The oligospermia and infertility..." has been deleted.

Based on the June 2, 1997 discussion referenced above, this is an acceptable revision, since this information is contained in the CLINICAL PHARMACOLOGY section, Clinical Studies subsection.

6. ADVERSE REACTIONS section:

a. In the first paragraph, the phrase "about 1830" [patients] has been revised to "3685."

Based on the June 2, 1997 discussion referenced above, the number of patients should be completely removed (since it is often a continually changing number) so that the first sentence reads, "Asacol tablets have been evaluated in inflammatory bowel disease patients (most patients with ulcerative colitis)..."

b. The following paragraph has been added,

"In a 6-month placebo-controlled maintenance trial involving 264 patients, 177 of whom were randomized to **Asacol** tablets, six (3.4%) of the **Asacol** patients discontinued **Asacol** therapy because of adverse events, as compared to four (4.6%) of the placebo patients. Adverse reactions leading to withdrawal from **Asacol** tablets included (each in one patient): anxiety; headache; pruritus; decreased libido; rheumatoid arthritis; and stomatitis and asthenia."

Based on the June 2, 1997 discussion referenced above, this is an acceptable revision.

c. The sentence,

> "Adverse events occurring at a frequency of 2% or greater in the two short-term, double-blind, placebo-controlled trials...,"

has been revised to read,

> "Adverse events occurring in Asacol-treated patients at a frequency of 2% or greater in the two short-term, double-blind, placebo-controlled

trials..."

Based on the June 2, 1997 discussion referenced above, this is an acceptable revision.

d. The title of Table 1 has been revised from

"Frequency (%) of Common Adverse Events Reported in Ulcerative Colitis Patients Treated with Asacol Tablets or Placebo in Double-Blind Controlled Studies,"

to

"Frequency (%) of Common Adverse Events Reported in Ulcerative Colitis Patients Treated with Asacol Tablets or Placebo in Short-Term (6-Week) Double-Blind Controlled Studies."

This is an acceptable revision.

e. The paragraph which reads, "Of these adverse events, only rash showed a consistently higher frequency with increasing Asacol dose in these studies. In uncontrolled data, fever, flu syndrome, and headache also seemed dose related," has been deleted.

Based on the June 2, 1997 discussion referenced above, the firm should be instructed to retain the first sentence in the paragraph, since no documentation supporting the deletion was provided; deletion of the remainder is an acceptable revision, since these adverse events are reflected elsewhere in the insert.

f. The sentence, "In addition, the following adverse reactions were seen in 1-2% of the patients in the controlled studies: malaise, arthritis, increased cough, acne, and conjunctivitis," has been deleted. Each of the adverse events has been moved to Table 1.

In a May 19, 1997 telephone conversation, Melanie Bruno, Ph.D., M.B.A., Regulatory Affairs, Procter and Gamble Pharmaceuticals, indicated that these adverse events had an incidence of 1.97% in the controlled trials, referenced above. According to Dr. Bruno, the firm decided to round this figure to 2% and, consequently, to include these adverse events in Table 1. Based on this conversation, this is an acceptable revision.

g. The following paragraph has been added,

"In the 6-month placebo-controlled maintenance trial, the incidence of adverse events seen with **Asacol** tablets was similar to that seen with placebo. In addition to events listed in Table 1, the following adverse events occurred in **Asacol**-treated patients at a frequency of 2% or greater in this study: abdominal enlargement, anxiety, bronchitis, ear disorder, ear pain, gastroenteritis, gastrointestinal hemorrhage, infection, joint disorder, migraine, nervousness, paresthesia, rectal disorder, rectal hemorrhage, sinusitis, stool abnormalities, tenesmus, urinary frequency, vasodilation, and vision abnormalities."

Based on the June 2, 1997 discussion referenced above, this is an acceptable revision.

h. The paragraph which begins, "Over 1800 patients have been treated...," has been deleted.

Based on the June 2, 1997 discussion referenced above, the firm should be instructed to retain the paragraph at this time, since no documentation has been submitted to support this revision.

i. The following paragraph has been added,

"In 3342 patients in uncontrolled clinical studies, the following adverse events occurred at a frequency of 5% or greater and appeared to increase in frequency with increasing dose: asthenia, fever, flu syndrome, pain, abdominal pain, back pain, flatulence, gastrointestinal bleeding, arthralgia, and rhinitis."

Based on the June 2, 1997 discussion referenced above, this is an acceptable revision, however, the firm should be requested to delete the number from the first sentence, since it is subject to change.

j. Immediately before the body system subsection, the statement, "In addition to the adverse events listed above, the following events have been reported with Asacol use," has been added.

This is an acceptable editorial revision.

k. The following adverse events have been moved from their respective body system subsections (in parentheses) to the paragraph described above in point g: abdominal enlargement (Body as a Whole), vasodilation, migraine (Cardiovascular), gastroenteritis, tenesmus (Digestive), anxiety, nervousness, paresthesia (Nervous); sinusitis (Respiratory/Pulmonary); and ear pain (Special Senses).

The currently approved wording should be retained, since justification for the revision was not provided. The firm should be asked to indicate why these adverse events (which were already part of the currently approved labeling) should be moved to a paragraph in the insert which is exclusively devoted to adverse events reported in the six month maintenance trial.

l. "Weakness" has been moved from its current position in the Body as a Whole subsection to the paragraph described above in point i and changed to "asthenia."

According to the twenty-sixth edition of Dorland's Illustrated Medical Dictionary, "asthenia" and "weakness" are synonyms, therefore, this is an acceptable revision.

l. "Insomnia" has been moved from its current location in the Nervous body system subsection to Table 1.

According to the May 19, 1997 telephone conversation with Dr. Bruno this adverse event had an incidence of 1.97% in the controlled trials, referenced above. According to Dr. Bruno, the firm decided to round this figure to 2% and, consequently, to add "insomnia" to Table 1. Therefore, this is an acceptable revision.

Note: In the June 2, 1997 discussion described above, it was decided that the firm should be asked to rearrange the ADVERSE REACTIONS section of the insert so that paragraphs which relate to the short term studies should be grouped together, separately from those related to the maintenance study. (See attached marked-up draft labeling)

7. OVERDOSAGE section:

This section has been revised from,

"One case of overdosage has been reported. A 3-year old male ingested 2 grams of Asacol tablets...,"

to

"Two cases of pediatric overdosage have been reported. A 3-year-old male who ingested 2 grams of **Asacol** tablets was treated with ipecac and activated charcoal; no adverse events occurred. Another 3-year-old male, approximately 16 kg, ingested an unknown amount of a maximum of 24 grams of **Asacol** crushed in solution (i.e.,uncoated mesalamine); he was treated with orange juice and activated charcoal, and experienced no adverse events. In dogs, single doses of 6 grams of delayed-release **Asacol** tablets resulted in renal papillary

necrosis but were not fatal. This was approximately 12.5 times the recommended human dose (based on a dose of 2.4 g/day in a 50 kg person). Single oral doses of uncoated mesalamine in mice and rats of 5000 mg/kg and 4595 mg/kg, respectively, or of 3000 mg/kg in cynomolgus monkeys, caused significant lethality.

Based on the June 2, 1997 discussion referenced above, this is an acceptable revision.

8. DOSAGE AND ADMINISTRATION section:

a. This section has been further divided into two subsections entitled, "For the treatment of mildly to moderately active ulcerative colitis" and "For the maintenance of remission of ulcerative colitis."

This is an acceptable editorial revision.

b. Maintenance of remission subsection: This new subsection reads, "The usual dosage in adults is one 400-mg tablet to be taken two times a day for a total daily dose of 0.8 grams. In some patients a higher daily dose of 1.6 grams, or four 400-mg tablets in divided doses, may be required."

Based on the June 2, 1997 discussion referenced above, all reference to the 0.8 gm/day dose should be deleted, and the firm should be requested to revise this subsection to read,

For the maintenance of remission of ulcerative colitis:

The recommended dosage in adults is 1.6 grams daily, administered as four 400 mg tablets in divided doses. Safety and efficacy beyond six months of therapy have not been established.

9. Storage Statement: This has been revised from "Store at Controlled room temperature (59°- 86°F or 15°- 30°C)." to "Store at controlled room temperature 20°- 25°C (68°- 77°F)[See USP]."

According to Dr. Eric Duffy, chemistry team leader, this is an acceptable revision.

10. Manufacturer/Distributor Block: The following patent numbers have been added, "U.S. Patent Nos. 5.541,170 and 5,541,171."

This is an acceptable editorial revision.

Conclusions

The firm should be requested to revise the insert as indicated above and reflected in the attached marked-up draft labeling. An approvable pending final printed labeling (FPL) letter should be drafted.

APPEARS THIS WAY
ON ORIGINAL

/S/ 6/5/97
Regulatory Health Project Manager

cc:
/S/ 6-5-97
Original NDA 19-651/S-005
HFD-180/Div. Files
HFD-180/MMcNeil
HFD-180/RPrizont
HFD-720/WChen
HFD-720/MHuque
HFD-180/JChoudary

draft: mm/May 29, 1997/c:\wpfiles\cso\reviews\19651705.ae
r/d Initials: KJohnson 6/3/97, 6/4/97
RPrizont 6/3/97

APPEARS THIS WAY
ON ORIGINAL

final: June 5, 1997

CSO REVIEW

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 19-651/S-005 AUG 18 1997

Name of Drug: Asacol (mesalamine) Tablets

Sponsor: Procter & Gamble Pharmaceuticals, Inc.

Material Reviewed

Submission Date(s): August 5, 1997, Final Printed Labeling

Receipt Date(s): August 6, 1997

Background and Summary Description: NDA 19-651/S-005 was submitted June 4, 1996 and provides for a new indication: the maintenance of remission in ulcerative colitis (UC). The application was Approvable pending FPL on June 5, 1997 and the action letter contained marked-up draft labeling.

Note: In response to the June 5, 1997 Approvable letter, the firm submitted revised draft labeling on June 17 and July 3, 1997. This labeling was discussed with Drs. Robert Prizont, medical reviewer and Lilia Talarico, Acting Division Director, and their comments were conveyed to Dr. Melanie Bruno, Regulatory Affairs, Procter & Gamble by telephone on July 2 and 15, 1997.

Review

The submitted insert **(coded 44003462, Revised July 1997)**, was compared to the marked-up draft insert which was enclosed with the June 5, 1997 Approvable letter. All changes can either be considered editorial or were mutually agreeable to the firm and the Agency as of the July 2 and 15, 1997 teleconferences.

Note: As indicated in the CSO labeling review dated June 5, 1997, the firm should be requested to revise the first sentence of the bolded statement in the PRECAUTIONS section, Renal subsection to read, "Therefore, caution should be exercised when using Asacol (or other compounds which contain or are converted to mesalamine or its metabolites) in patients with known renal dysfunction or history of renal disease." This request was inadvertently omitted from the marked-up draft labeling which accompanied the Approvable letter. However, in a August 18, 1997 telephone conversation, Dr. Bruno, on behalf of Procter & Gamble Pharmaceuticals, agreed to make this revision at the next printing of the insert.

Conclusions

The labeling is acceptable as submitted, however, it will be revised at the next printing to incorporate the modification to the PRECAUTIONS section, Renal subsection, as discussed above. An Approval letter should be drafted.

/S/ 8/18/97

Regulatory Health Project Manager

APPEARS THIS WAY

Concur,

8-18-97

/S/

cc:

Original 19-651/S-005
HFD-180/Div. Files
HFD-180/MMcNeil
HFD-180/Prizont
HFD-80/Choudary

draft: mm/August 18, 1997/c:\wpfiles\cso\reviews\19651708.slr
final: August 18, 1997

CSO REVIEW

McNeil

MEMORANDUM OF MEETING MINUTES

Meeting Date: November 19, 1996
Time: 10-11 AM
Location: Conference Room 6B-45 (PKLN)

Application: NDA 19-651/SE1-005

Type of Meeting: Five Month Team Meeting

Meeting Chair: Dr. Stephen B. Fredd

Meeting Recorder: Melodi McNeil, CSO

FDA Attendees, titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Dr. Stephen Fredd, Division Director
Dr. Robert Prizont, Reviewing Medical Officer
Dr. Jasti Choudary, Pharmacology Team Leader
Dr. Ke Zhang, Reviewing Pharmacologist
Ms. Melodi McNeil, Consumer Safety Officer
Ms. Kati Johnson, Consumer Safety Officer

Division of Biometrics, (HFD-720)
Dr. Mo Huque, Statistics Team Leader
Dr. Wen-jen Chen, Reviewing Statistician

Background: This application was submitted June 4, 1996 and provides for a new indication: the maintenance of remission in ulcerative colitis (UC). The firm has initially proposed a dose of 800-1600 mg per day in divided doses.

As pivotal efficacy support, the firm has submitted a double-blind, randomized withdrawal study which compares two doses of Asacol (800 and 1600 mg) to placebo (PBO). In addition, the firm has submitted a meta analysis of four positive control studies comparing Asacol to sulfasalazine.

Meeting Objective: To update review team members as to the status of the reviews.

Discussion Points:

1. Administrative:

   Dr. Fredd observed that this application will be signed off at the Division level and commented that it was unlikely to go to an advisory committee, unless the team suggested otherwise.

Dr. Fredd noted the June 5, 1997 user fee due date and requested that a team meeting be held on approximately April 15, 1997 to resolve any outstanding labeling issues. In order to achieve this goal, he requested that all reviews be finalized by the second week in April.

2. Statistics:

   a. Carcinogenicity:

      Dr. Chen is awaiting the receipt of carcinogenicity data on diskette. Once this information is received, he will inform Dr. Choudary as to when the carcinogenicity portion of the statistics review will be complete so that Dr. Choudary can schedule a meeting to present the studies to the Carcinogenicity Assessment Committee's (CAC) executive committee.

   b. Clinical:

      Dr. Chen said his analyses revealed similar results as the sponsor's, though he noted that he had not completed his review of the firm's meta analysis yet. Dr. Fredd asked that Dr. Chen's analysis include a variety of covariates, including, but not limited to concomitant drug use, age, gender, smoking status, etc.

3. Pharmacology:

   Dr. Choudary said that the first draft of the pharmacology review has been completed, and no major problems have been identified thus far. Dr. Zhang will require input from the statistician with respect to the carcinogenicity studies before the review can be finalized.

4. Clinical:

   Dr. Prizont noted that in the intent to treat (ITT) population of the PBO study (study# 87086), statistical significance was achieved for both doses of Asacol and said, in general, the conduct of the study appears acceptable.

   Dr. Fredd commented that a problem with this application is the potential lack of replication if the meta analysis does not support approval.

5. Chemistry:

Note: Dr. Arthur Shaw is reviewing the environmental assessment (EA) and comparative composition data (currently approved formulation of Asacol vs. formulations used in the clinical trials) for this application.

It was decided that Ms. McNeil will contact Dr. Arthur Shaw, Reviewing Chemist, and communicate any major problems with the application, from a chemistry, manufacturing, and controls perspective, to Dr. Fredd.

Conclusions:

1. Dr. Fredd requested that all reviews be finalized by the second week of April.

2. At Dr. Fredd's suggestion, the next team meeting for this application will be held on approximately April 15, 1997 to discuss labeling issues, unless another review team member desires additional meetings.

Minutes Preparer: /S/ 11/26/96

Chair Concurrence: /S/ 11/26/96

Attachments/Handouts: None

cc: Original NDA 19-651/SE1-005
HFD-180/Div. Files
HFD-180/Minutes Files
HFD-180/CSO and attendees
HFD-180/AShaw

drafted: November 19, 1996
r/d initials: KJohnson 11/25/96
final: November 26, 1996

MEETING MINUTES

mcneil

MEMORANDUM OF TELECON

DATE: March 4 and March 5, 1997

APPLICATION NUMBER: NDA 19-651/SE1-005; Asacol® Delayed Release Tablets

BETWEEN:

Name: Melanie Bruno and Burney Schwab
Phone: 513 626-1148
Representing: Procter and Gamble

AND

Name: Arthur B. Shaw, Ph.D.
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: This call was in response to a request for information about the manufacturing sites for this drug product for the EA. Mr. Schwab acknowledged that the original EA is very sketchy. It is included in its entirety in Appendix E of the amendment dated January 24, 1997. The manufacture of the drug product is covered by a DMF. I checked for this in They will send a summary description of the

/S/ 3/12/97

APPEARS THIS WAY

Arthur B. Shaw, Ph.D.
Review Chemist

cc: Original NDA 19-651/SE1-005
HFD-180/Div. File
HFD-180/Arthur B. Shaw, Ph.D.
HFD-180/EDuffy
HFD-181/MMcNeil
R/D init: EDuffy/3-6-97
ABS/dob **F/T 3-12-97**\WP: c:\wpfiles\chem\S\19651005.AS1

APPEARS THIS WAY

/S/ 3/19/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019651/S005

CORRESPONDENCE

mcneil

NDA 19-651/S-005

MAY - 2 1997

Procter & Gamble Pharmaceuticals
Attention: Melanie A. Bruno, Ph.D., M.B.A.
11450 Grooms Road
SW GR DNW-36 Box# C30
Cincinnati, OH 45242-1408

Dear Dr. Bruno:

Please refer to your pending June 4, 1996 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Asacol (mesalamine) Tablets.

We also refer to your amendment dated April 4, 1997, containing the response to our letter dated March 31, 1997. In the March 31, 1997 letter we requested information about Study # **87086** entitled, "An Oral Preparation Of Mesalamine As Long-Term Maintenance Therapy For Ulcerative Colitis: A Randomized, Placebo-Controlled Trial," in which patients were administered Asacol 0.8 gm/day, Asacol 1.6 gm/day, or placebo (PBO).

To complete our review of your submission, we have the following additional requests:

1. Please provide the efficacy data sets (Data Set #1 and Data Set #2) in the following format:

Data Set #1:

center
treatment
eaton: patient #
itt: patient in the ITT data set (Y/N)
ptcomp: patient completed study (Y/N)
visit #
sched: endoscopy within visit window (Y/N) [based on each visit]
outcome: treatment success (Y/N) [at the visit]

Data Set #2

center
treatment
eaton: patient #
itt: patient in the ITT data set (Y/N)
ptcomp: patient completed study (Y/N)
overall-sched: patient-endoscopies all within visit-windows (Y/N)
outcome: treatment success (Y/N) [as in the original June 4, 1996 submission]

2. Please provide statistical analysis (e.g. Mantel-Haenszel test) on Data Set #2 using overall-sched as a stratum covariate to compare the treatment effects for both ITT and completed data sets including a test for treatment by covariate interaction.

We would appreciate your prompt written response so we can continue our evaluation of your supplemental application. Your response should be submitted in duplicate (Archival [blue] and Statistical [green]). In addition, please provide the data from the statistical analysis on SAS diskettes, as 6.10 files (extension .sd2).

If you have any questions, please contact Melodi McNeil, Regulatory Health Project Manager, at (301) 443-0483.

Sincerely yours,

/S/ 5-2-97 /S/ 5/2/97

APPEARS THIS WAY ON ORIGINAL

Lilia Talarico, M.D.
Acting Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 19-651/S-005
HFD-180/Div. Files
HFD-180/CSO/M.McNeil
HFD-180/Prizont
HFD-720/Huque
HFD-720/Chen

APPEARS THIS WAY ON ORIGINAL

Drafted by: mm/April 25, 1997/c:\wpfiles\cso\n\19651704.ir
Initialed by: KJohnson 5/2/97
LTalarico 5/2/97 /S/ 5-2-97
final: May 2, 1997

INFORMATION REQUEST (IR)

McNeil

NDA 19-651/S-005

Procter & Gamble Pharmaceuticals
Attention: Melanie Bruno, Ph.D., M.B.A.
11450 Grooms Road
Cincinnati, OH 45242

JUN 12 1996

Dear Dr. Bruno:

We acknowledge receipt of your supplemental application for the following:

Name of Drug Product: Asacol (mesalamine) Tablets

NDA Number: NDA 19-651

Supplement Number: S-005

Therapeutic Classification: Standard

Date of Supplement: June 4, 1996

Date of Receipt: June 5, 1996

This supplement provides for a new indication, the maintenance of remission of ulcerative colitis.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on August 4, 1996 in accordance with 21 CFR 314.101(a).

All communications concerning this supplemental application should be addressed as follows:

APPEARS THIS WAY ON ORIGINAL

Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: DOCUMENT CONTROL ROOM
5600 Fishers Lane
Rockville, Maryland 20857

Should you have any questions, please contact me at (301) 443-0483.

cc:
Original NDA 19-651/S-005
HFD-180/Div. Files
HFD-180/CSO/M.McNeil
DISTRICT OFFICE

/S/ 6/12/96

drafted: mm/June 7, 1996/c:\wpfiles\cso\n\19651606.ack
RD Init: KJohnson 6/11/96
Final: June 11, 1996

SUPPLEMENT ACKNOWLEDGEMENT

Sincerely yours,

/S/ 6-11-96

Melodi McNeil
Consumer Safety Officer
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Procter&Gamble
PHARMACEUTICALS

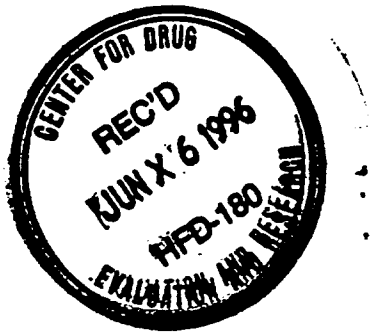
The Procter & Gamble Company
Sharon Woods Technical Center
11450 Grooms Road, Cincinnati, Ohio 45242-1434

file date = 8-4-96
goal date = 6-5-97

June 4, 1996

19-651/S-005

Dr. Stephen B. Fredd, M.D., Director
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
ATTN: Document Control Room #6B-24
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



RE: NDA#19-651, Asacol (mesalamine) Delayed-Release Tablets
Supplemental New Drug Application, Supplement #5
Seeking Maintenance of Remission of Ulcerative Colitis Indication for Asacol

Dear Dr. Fredd,

Pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act, Procter & Gamble Pharmaceuticals is submitting this Supplemental New Drug Application for the Maintenance of Remission of Ulcerative Colitis indication for Asacol® (mesalamine) Delayed-Release Tablets. This represents the fifth supplement submitted to this NDA.

Procter & Gamble Pharmaceuticals has been assigned a User Fee number and has remitted a check for to the Food and Drug Administration Offices associated with

Please contact me if there are any questions regarding this application.

Sincerely yours,

Melanie A. Bruno

Melanie A. Bruno, Ph.D., M.B.A.
Regulatory Affairs
Procter & Gamble Pharmaceuticals
Phone (513) 626-1148
Fax (513) 626-4414

Attachment: box shipping information

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 17, 1996

FROM: Pharmacology Team Leader
Division of Gastrointestinal and
Coagulation Drug Products, HFD-180

SUBJECT: NDA 19,651 (Asacol Delayed Release Tablets)
Supplement (SE1 005) Dated June 4, 1996 -
Deficiencies.

TO: NDA 19,651

The following deficiencies are noted in the submission. The assigned Pharmacologist (Dr. Zhang) may find additional deficiencies.

1. The submission contains one report each of a carcinogenicity study in mice and rats. There is also a second rat carcinogenicity study (E3) listed in Table 14 on page 306 of Volume 35.1 and Table 26 on page 68 of Volume 35.2. In both tables it is noted as "Study ongoing: In-life complete. Report will be submitted upon completion." No other information could be located in the submission. Sponsor should be asked to provide full information and clarifications on this ongoing study.

2. The mouse (CD-1) carcinogenicity study (E1, Volumes 35.18 to 35.28) was conducted during the period of 1993 to 1995 in P & G facilities at Norwich, N.Y. Historical control data for tumor incidences could not be located. Sponsor should be asked to provide historical control data of tumor incidences from the same testing laboratory for the period of 1991 to 1995.

3. The rat (Sprague-Dawley) carcinogenicity study (E2, Volumes 35.29 to 35.39) was conducted during the period of 1992 to 1994 in the P & G facilities at Norwich, N.Y. Historical control data for tumor incidences could not be located. Sponsor should be asked to provide historical control data from the same testing laboratory for the period of 1990 to 1994.

4. Sponsor should be asked to provide Tables of incidences of tumors of hematopoietic system by tumor type (whole body counts) e.g. lymphoma, histiocytic sarcoma etc. for both species.

5. Sponsor should be asked to provide English versions of foreign language publications included in the submission. For example, no English translation is available for the following:

Ayo Yakari 48(6): 501-509, 1994
Mutagenicity Study of Mesalazine (Volume 35.41, pages 56 to 64).

/S/
Jasti B. Choudary, Ph.D., B.V.Sc.

cc:
NDA
HFD-180
HFD-181/CSO
HFD-180/Dr. Choudary
HFD-180/Dr. Fredd
HFD-180/Dr. Zhang

JBC/hw/6/17/96
C:\WPFILES\PHARM\N\19651606.0JC

APPEARS THIS WAY
ON ORIGINAL